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=> s antibody
L1 2342002 ANTIBODY

=> s l1 and monoclonal
L2 696469 L1 AND MONOCLONAL

=> s l2 and connective tissue growth factor
L3 0 L2 AND CONNECTIVE TISSUE GRWOTH FACTOR

=> s l2 and CTGF
L4 34 L2 AND CTGF

=> s l4 and crossreact
L5 0 L4 AND CROSSREACT

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L6 10 L4 AND MOUSE

=> s l6 and human
L7 10 L6 AND HUMAN

=> s l7 and rat
L8 1 L7 AND RAT

=> d l8 cbib abs

L8 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
1999:460440 Document No. 131:101260 **Monoclonal antibody**
against connective tissue growth factor and medicinal uses thereof.
Tamatani, Takuya; Tezuka, Katsunari; Sakamoto, Shinji; Takigawa, Masaharu
(Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9933878 A1 19990708, 212
pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA,
CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183 19981215.

AB Disclosed is a **human monoclonal antibody** useful for remedying various diseases caused by **human** connective tissue growth factor (hCTGF), and preventing the onset of hCTGF-assocd. diseases. Also, disclosed are various **monoclonal antibodies** having various characteristics against various mammalian connective tissue growth factors (mCTGFs) useful for detecting and assaying mCTGFs present in the body fluids of mammals suffering from mCTGF-assocd. diseases. The **CTGF-assocd.** diseases include cell proliferation-accompanying diseases of or fibrosis of lung, hear, liver, kidney, brain, neck, pancreas, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue, and blood vessel. Thus, **human CTGF** (242-252) peptide Cys-Glu-Ala-Asp-Leu-Glu-Glu-Asn-Ile-Lys was synthesized and mixed with Freund's complete adjuvant for immunization to raise polyclonal **antibody** in rabbits. Similarly, **monoclonal anti-hCTGF** and **mouse CTGF antibodies** and producing hybridomas were prep'd. Prep'd. **antibodies** were tested for cross binding reactivity and were used for affinity (column) chromatog. purifn. of mammalian **CTGFs** and treatment of tissue fibrosis in **mice** model. Mol. cloning of prep'd. **human monoclonal anti-hCTGF antibody** was performed and sequences of single (heavy and light) chain fragments were detd. ELISA with the prep'd. **antibodies** and fragments was used for detecting serum or synovial **CTGF** in patients with biliary duct obstruction, rheumatoid vasculitis, malignant rheumatoid arthritis, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 18:16:35 ON 05 SEP 2002

L1 2342002 S ANTIBODY
L2 696469 S L1 AND MONOCLONAL
L3 0 S L2 AND CONNECTIVE TISSUE GRWOTH FACTOR
L4 34 S L2 AND CTGF
L5 0 S L4 AND CROSSREACT
L6 10 S L4 AND MOUSE
L7 10 S L6 AND HUMAN
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L9 10 L4 AND MOUSE

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L10 6 DUP REMOVE L9 (4 DUPLICATES REMOVED)

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L10 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:299415 Document No.: PREV200100299415. Integrin alphaMbeta2 acts as an adhesion receptor on peripheral blood monocytes and THP-1 cells for Cyr61 and connective tissue growth factor. Schober, Joseph M. (1); Lau, Lester

F.; Ye, Richard (1); Ugarova, Tatiana P.; Lam, Stephen C.-T. (1). (1) Pharmacology, University of Illinois, Chicago, IL USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 18a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB Cyr61 and connective tissue growth factor (**CTGF**) are growth factor-inducible immediate-early gene products found in normal blood vessel walls, advanced atherosclerotic lesions and healing cutaneous wounds. We previously showed that the adhesion of endothelial cells, platelets and fibroblasts to these matricellular proteins is mediated by integrin receptors. Because monocyte adhesion is important for inflammation, wound healing and atherosclerosis, we examined the adhesion of isolated peripheral blood monocytes (PBMC) and THP-1 cells to microtiter wells coated with Cyr61 or **CTGF**. Both PBMC and THP-1 cells adhered in a dose-dependent manner to Cyr61- and **CTGF**-coated wells. Moreover, stimulation of THP-1 cells with 20 μ M ADP caused a 6- to 10-fold increase in cell adhesion to both proteins. Time course studies showed that THP-1 cell adhesion to Cyr61 was transient, peaking at 20-30 minutes and declining thereafter. In inhibition studies, while EDTA completely blocked THP-1 cell adhesion to Cyr61, GRGDSP and echistatin had no effect. These data suggest the involvement of an RDG-insensitive integrin receptor. Using **monoclonal antibodies** specific for integrin subunits, we found that the adhesion of THP-1 cells and PBMC to Cyr61 and **CTGF** was specifically blocked by YFC118.3 (anti-beta2), and by 44a and 2LPM19c (anti-alphaM). In contrast, **mouse** IgG and 6S6 (anti-beta1) had no effect. Thus, monocyte adhesion to Cyr61 and **CTGF** is mediated by integrin alphaMbeta2. Consistent with the cell adhesion data, a GST-fusion protein containing the I-domain of the alphaM subunit bound specifically to immobilized Cyr61 and **CTGF**, and the binding was completely blocked by 2LPM19c (anti-alphaM) but not by YFC118.3 (anti-beta2). Collectively, these results identified integrin alphaMbeta2 as an adhesion receptor on monocytes for Cyr61 and **CTGF**. Since these proteins are synthesized by vascular smooth muscle cells, the interaction of monocytes with these novel extracellular matrix proteins may have an important implication in the physiological function of monocytes.

L10 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS

1999:460440 Document No. 131:101260 **Monoclonal antibody** against connective tissue growth factor and medicinal uses thereof. Tamatani, Takuya; Tezuka, Katsunari; Sakamoto, Shinji; Takigawa, Masaharu (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9933878 A1 19990708, 212 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIIXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183 19981215.

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blood vessel. Thus, human **CTGF** (242-252) peptide Cys-Glu-Ala-Asp-Leu-Glu-Glu-Asn-Ile-Lys was synthesized and mixed with Freund's complete adjuvant for immunization to raise polyclonal **antibody** in rabbits. Similarly, **monoclonal** anti-hCTGF and **mouse CTGF antibodies** and producing hybridomas were prep'd. Prep'd. **antibodies** were tested for cross binding reactivity and were used for affinity (column) chromatog. purifn. of mammalian **CTGFs** and treatment of tissue fibrosis in **mice** model. Mol. cloning of prep'd. human **monoclonal** anti-hCTGF **antibody** was performed and sequences of single (heavy and light) chain fragments were detd. ELISA with the prep'd. **antibodies** and fragments was used for detecting serum or synovial **CTGF** in patients with biliary duct obstruction, rheumatoid vasculitis, malignant rheumatoid arthritis, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis.

L10 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2002 ACS

1999:299520 Document No. 130:321593 Cloning and cDNA sequences for human and murine Wnt-1-induced secreted (WISP) polypeptides. Botstein, David A.; Cohen, Robert L.; Gurney, Austin L.; Hillan, Kenneth; Lawrence, David A.; Levine, Arnold J.; Pennica, Diane; Roy, Margaret Ann; Goddard, Audrey; Wood, William I. (Genentech, Inc., USA). PCT Int. Appl. WO 9921998 A1 19990506, 284 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US22991 19981029. PRIORITY: US 1997-63704 19971029; US 1998-73612 19980203; US 1998-81695 19980414.

AB Wnt-1-induced secreted proteins (WISPs) are provided, whose genes are induced at least by Wnt-1. Several putative Wnt-1-induced genes (WISP1, WISP2, WISP3) were identified at the mRNA level in a high-throughput cDNA subtraction expt. The cDNA clones encode novel polypeptides having homol. to **CTGF**. The genes downstream of Wnt-1 signaling in vertebrates presumably function in tumorigenesis. WISP-1 is expressed in embryonic skeletal mesenchyme and at sites of bone formation, is likely to play a role in osteogenesis, and may be involved in repair after injury. Also provided are nucleic acid mols. encoding those polypeptides, as well as vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide mols. comprising the polypeptides fused to heterologous polypeptide sequences, **antibodies** which bind to the polypeptides, and methods for producing the polypeptides.

L10 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2002 ACS

1999:220010 Document No. 130:251226 Neovascularization inhibitor. Takigawa, Masaharu; Nakanishi, Tohru; Shimo, Tsuyoshi (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9913910 A1 19990325, 53 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP4124 19980911. PRIORITY: JP 1997-267943 19970912; JP 1998-267388 19980904.

AB A medicinal compn. contg. an **antibody** having a reactivity with human **CTGF** (connective tissue growth factor) has been found out to inhibit the proliferation and migration of vascular endothelial cells and, moreover, neovascularization. It is highly useful in treating diseases and symptoms caused by the proliferation and migration of vascular endothelial cells or neovascularization (for example, diabetic

retinopathy, arteriosclerosis, arterial constriction, chronic articular rheumatism, psoriasis, sclerema, glaucoma, proliferation or metastasis of tumor, and inflammation in various organs). Thus, recombinant human **CTGF** was constructed, expressed in HeLa cells, and tested for vascular endothelial cell proliferation and migration-promoting activity. Rabbit **monoclonal** anti-human **CTGF** **antibody** was prep'd. using CEADLEIK as immunogen, and tested for vascular endothelial cell proliferation and migration-inhibiting activity. In addn., transgenic **mice** were used for raising human **monoclonal** anti-human **CTGF** **antibodies** and hybridomas producing them.

L10 ANSWER 5 OF 6 MEDLINE DUPLICATE 1
1999377072 Document Number: 99377072. PubMed ID: 10446209.
Activation-dependent adhesion of human platelets to Cyr61 and Fisp12/
mouse connective tissue growth factor is mediated through integrin
alpha(IIb)beta(3). Jedsadayanmata A; Chen C C; Kireeva M L; Lau L F; Lam S
C. (Department of Pharmacology, University of Illinois, Chicago, Illinois
60612, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Aug 20) 274 (34)
24321-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United
States. Language: English.
AB Cyr61 and connective tissue growth factor (**CTGF**), members of a
newly identified family of extracellular matrix-associated signaling
molecules, are found to mediate cell adhesion, promote cell migration and
enhance growth factor-induced cell proliferation in vitro, and induce
angiogenesis in vivo. We previously showed that vascular endothelial cell
adhesion and migration to Cyr61 and Fisp12 (**mouse** **CTGF**)
) are mediated through integrin alpha(v)beta(3). Both Cyr61 and
Fisp12/mCTGF are present in normal blood vessel walls, and it has been
demonstrated that **CTGF** is overexpressed in advanced
atherosclerotic lesions. In the present study, we examined whether Cyr61
and Fisp12/mCTGF could serve as substrates for platelet adhesion. Agonist
(ADP, thrombin, or U46619)-stimulated but not resting platelets adhered to
both Cyr61 and Fisp12/mCTGF, and this process was completely inhibited by
prostaglandin I(2), which prevents platelet activation. The specificity of
Cyr61- and Fisp12/mCTGF-mediated platelet adhesion was demonstrated by
specific inhibition of this process with polyclonal anti-Cyr61 and
anti-Fisp12/mCTGF **antibodies**, respectively. The adhesion of
ADP-activated platelets to both proteins was divalent cation-dependent and
was blocked by RGDS, HHLGGAKQAGDV, or echistatin, but not by RGES.
Furthermore, this process was specifically inhibited by the
monoclonal antibody AP-2 (anti-alpha(IIb)beta(3)), but
not by LM609 (anti-alpha(v)beta(3)), indicating that the interaction is
mediated through integrin alpha(IIb)beta(3). In a solid phase binding
assay, activated alpha(IIb)beta(3), purified by RGD affinity
chromatography, bound to immobilized Cyr61 and Fisp12/mCTGF in a
dose-dependent and RGD-inhibitable manner. In contrast, unactivated
alpha(IIb)beta(3) failed to bind to either protein. Collectively, these
findings identify Cyr61 and Fisp12/mCTGF as two novel activation-dependent
adhesive ligands for the integrin alpha(IIb)beta(3) on human platelets,
and implicate a functional role for these proteins in hemostasis and
thrombosis.

L10 ANSWER 6 OF 6 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998379823 EMBASE Establishment of the enzyme-linked immunosorbent assay for
connective tissue growth factor (**CTGF**) and its detection in the
sera of biliary atresia. Tamatani T.; Kobayashi H.; Tezuka K.; Sakamoto
S.; Suzuki K.; Nakanishi T.; Takigawa M.; Miyano T.. T. Tamatani,
Pharmaceutical Frontier Research Lab, JT Inc., 1-13-2 Fukuura, Yokohama,
Kanagawa 236-0004, Japan. tamatani@ikrl.jti.co.jp. Biochemical and
Biophysical Research Communications 251/3 (748-752) 29 Oct 1998.
Refs: 23.
ISSN: 0006-291X. CODEN: BBRCA. Pub. Country: United States. Language:

AB English. Summary Language: English.
Connective tissue growth factor (**CTGF**) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine **monoclonal antibodies** against **CTGF** and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of **CTGF**. By using the ELISA, we confirmed that **CTGF** was specifically induced in human fibroblasts by TGF-.beta. but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of **CTGF** were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that **CTGF** is potentially a useful parameter for monitoring certain types of fibrotic disorders.

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FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 18:16:35 ON 05 SEP 2002

L1 2342002 S ANTIBODY
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L6 10 S L4 AND MOUSE
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L13 3 DUP REMOVE L12 (0 DUPLICATES REMOVED)

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L13 ANSWER 1 OF 3 MEDLINE
2002322970 Document Number: 22061083. PubMed ID: 12065687. Effects and regulation of connective tissue growth factor on hepatic stellate cells. Paradis Valerie; Dargere Delphine; Bonvouost Franck; Vidaud Michel; Segarini Patricia; Bedossa Pierre. (Service d'Anatomie Pathologique, Hopital de Bicetre, Le Kremlin-Bicetre, France.. vparadis@teaser.fr) . LABORATORY INVESTIGATION, (2002 Jun) 82 (6) 767-74. Journal code: 0376617. ISSN: 0023-6837. Pub. country: United States. Language: English.

AB Connective tissue growth factor (**CTGF**) is a 38-kd protein involved in several **human** fibrotic disorders including atherosclerosis and skin and renal fibrosis. Although it has been shown that **human** and experimental liver fibrosis is associated with **CTGF** expression through up-regulation of **CTGF** mRNA by hepatic stellate cells (HSC), the role of **CTGF** in the liver has not yet been determined. The aim of the present study was to assess the effects of **CTGF** on **rat** primary HSC and its regulation in a well-established model of in vitro liver fibrogenesis. Incubation of primary HSC with recombinant **CTGF** induced a significant migratory (2.3-fold, 50 ng/ml **CTGF**) and proliferative effect (1.8-fold, 100 ng/ml **CTGF**). Type I collagen mRNA expression, as

assessed by a real-time RT-PCR procedure, was also increased when cells were incubated in the presence of **CTGF** (2-fold, 50 ng/ml). Transforming growth factor-beta1 (TGF-beta1) strongly stimulated **CTGF** mRNA expression, a direct mechanism observed in the absence of any intermediate protein synthesis. Furthermore, spontaneous activation of HSC plated on plastic and stimulation by vascular endothelial growth factor, lipid peroxidation products (HNE, MDA), acetaldehyde, and platelet-derived growth factor (PDGF)-BB significantly up-regulated **CTGF** mRNA expression in HSC. PDGF-induced **CTGF** stimulation might be related in part to TGF-beta1 secretion because **CTGF** mRNA up-regulation observed after PDGF-BB stimulation was abrogated in the presence of neutralizing TGF-beta1 **antibody**. In conclusion, this study extends the role of **CTGF** in HSC activation and suggests that **CTGF** up-regulation might be a central pathway during HSC activation.

L13 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2002 ACS

1999:460440 Document No. 131:101260 **Monoclonal antibody**

against connective tissue growth factor and medicinal uses thereof. Tamatani, Takuya; Tezuka, Katsunari; Sakamoto, Shinji; Takigawa, Masaharu (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9933878 A1 19990708, 212 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183 19981215.

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L13 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2002 ISI (R)

1998:864155 The Genuine Article (R) Number: 136WM. Establishment of the enzyme-linked immunosorbent assay for connective tissue growth factor (CTGF) and its detection in the sera of biliary atresia. Tamatani T (Reprint); Kobayashi H; Tezuka K; Sakamoto S; Suzuki K; Nakanishi T; Takigawa M; Miyano T. JT INC, PHARMACEUT FRONTIER RES LABS, KANAZAWA KU,

1-13-2 FUKUURA, YOKOHAMA, KANAGAWA 236000, JAPAN (Reprint); JUNTENDO UNIV, SCH MED, DEPT PEDIAT SURG, BUNKYO KU, TOKYO 113, JAPAN; OKAYAMA UNIV, SCH DENT, DEPT BIOCHEM & MOL DENT, OKAYAMA 7008525, JAPAN. BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS (29 OCT 1998) Vol. 251, No. 3, pp. 748-752. Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS. 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495. ISSN: 0006-291X. Pub. country: JAPAN. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Connective tissue growth factor (**CTGF**) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine **monoclonal antibodies** against **CTGF** and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of **CTGF**. By using the ELISA, we confirmed that **CTGF** was specifically induced in **human** fibroblasts by TGF-beta but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of **CTGF** were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that **CTGF** is potentially a useful parameter for monitoring certain types of fibrotic disorders. (C) 1998 Academic Press.

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L14 13 DUP REMOVE L11 (7 DUPLICATES REMOVED)

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L14 ANSWER 1 OF 13 MEDLINE

2002322970 Document Number: 22061083. PubMed ID: 12065687. Effects and regulation of connective tissue growth factor on hepatic stellate cells. Paradis Valerie; Dargere Delphine; Bonvouost Franck; Vidaud Michel; Segarini Patricia; Bedossa Pierre. (Service d'Anatomie Pathologique, Hopital de Bicetre, Le Kremlin-Bicetre, France.. vparadis@teaser.fr) . LABORATORY INVESTIGATION, (2002 Jun) 82 (6) 767-74. Journal code: 0376617. ISSN: 0023-6837. Pub. country: United States. Language: English.

AB Connective tissue growth factor (**CTGF**) is a 38-kd protein involved in several **human** fibrotic disorders including atherosclerosis and skin and renal fibrosis. Although it has been shown that **human** and experimental liver fibrosis is associated with **CTGF** expression through up-regulation of **CTGF** mRNA by hepatic stellate cells (HSC), the role of **CTGF** in the liver has not yet been determined. The aim of the present study was to assess the effects of **CTGF** on rat primary HSC and its regulation in a well-established model of in vitro liver fibrogenesis. Incubation of primary HSC with recombinant **CTGF** induced a significant migratory (2.3-fold, 50 ng/ml **CTGF**) and proliferative effect (1.8-fold, 100 ng/ml **CTGF**). Type I collagen mRNA expression, as assessed by a real-time RT-PCR procedure, was also increased when cells were incubated in the presence of **CTGF** (2-fold, 50 ng/ml). Transforming growth factor-beta1 (TGF-beta1) strongly stimulated **CTGF** mRNA expression, a direct mechanism observed in the absence of any intermediate protein synthesis. Furthermore, spontaneous activation of HSC plated on plastic and stimulation by vascular endothelial growth factor, lipid peroxidation products (HNE, MDA), acetaldehyde, and platelet-derived growth factor (PDGF)-BB significantly up-regulated **CTGF** mRNA expression in HSC. PDGF-induced **CTGF** stimulation might be related in part to TGF-beta1 secretion because **CTGF** mRNA up-regulation observed after PDGF-BB stimulation was abrogated in the presence of neutralizing TGF-beta1 **antibody**. In conclusion, this study extends the role of **CTGF** in HSC activation and suggests that **CTGF** up-regulation might be a central pathway during HSC activation.

L14 ANSWER 2 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:314023 Document No.: PREV200100314023. Gene induction by coagulation factor Xa is mediated by activation of protease activated receptor-1. Riewald, Matthias (1); Kravchenko, Vladimir (1); Petrovan, Ramona J. (1); Brass, Lawrence F.; Ruf, Wolfram (1). (1) Dep of Immunology, The Scripps Research Institute, La Jolla, CA USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 447a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB In addition to activating prothrombin, the coagulation protease factor Xa (Xa) triggers a variety of cellular responses, including induction of inflammatory genes. We found that Xa and thrombin, but not other coagulation serine proteases, induced nuclear factor- κ B (NF- κ B) in a HeLa cell line that expresses protease activated receptor (PAR)-1, but not PAR-2, -3, and -4. Xa in the presence of the specific thrombin inhibitor hirudin induced NF- κ B in HeLa cells efficiently, but with delayed kinetic compared to thrombin. This delay caused no difference in gene expression patterns, as determined by high-density microarray analysis. Both proteases most prominently induced the angiogenesis promoting genes Cyr61 and connective tissue growth factor (**CTGF**) on the panel represented by the UniGEM V chip (Incyte Corp.). Inhibition of PAR-1 cleavage with **monoclonal antibodies** abolished MAP kinase phosphorylation and gene induction by Xa, demonstrating that Xa signals through PAR-1 and not through a novel member of the PAR family. The snake venom prothrombin-activating enzyme Ecarin also produced PAR-1 dependent signaling that was completely blocked by the thrombin inhibitor hirudin, demonstrating that prothrombin remained cell associated during serum starvation at levels that are sufficient to allow for PAR-1 activation. The efficacy of hirudin to block in situ generated thrombin excludes thrombin as an intermediate in Xa-dependent PAR-1 activation which was not inhibited by hirudin. The concentration dependence of Xa for PAR-1 activation is consistent with previously characterized Xa-mediated PAR-2 signaling, suggesting that local concentration of Xa on the cell surface, rather than sequence specific recognition of the PAR scissile bond is determining receptor cleavage. This study demonstrates that PAR-1 cleavage by Xa can elicit the same cellular response as thrombin, but mechanistic differences in receptor recognition may be crucial for specific roles for Xa in signaling in spatial or temporal separation from thrombin generation.

L14 ANSWER 3 OF 13 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000040274 EMBASE Serum levels of connective tissue growth factor are elevated in patients with systemic sclerosis: Association with extent of skin sclerosis and severity of pulmonary fibrosis. Sato S.; Nagaoka T.; Hasegawa M.; Tamatani T.; Nakanishi T.; Takigawa M.; Takehara K.. Dr. S. Sato, Department of Dermatology, Kanazawa Univ. School of Medicine, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan. s-sato@med.kanazawa-u.ac.jp. Journal of Rheumatology 27/1 (149-154) 2000.

Refs: 33.

ISSN: 0315-162X. CODEN: JRHUA. Pub. Country: Canada. Language: English.

Summary Language: English.

AB Objective. To determine the serum levels and clinical correlation of connective tissue growth factors (**CTGF**) in patients with systemic sclerosis (SSc). Methods. Serum samples from patients with limited cutaneous SSc (lSSc, n = 32), diffuse cutaneous SSc (dSSc, n = 28), systemic lupus erythematosus (SLE, n = 30), polymyositis/dermatomyositis (PM/DM, n = 20), and healthy control subjects (n = 30) were examined by ELISA for detection of **CTGF**. Results. Serum **CTGF** levels in patients with SSc were significantly higher than those in patients with SLE or PM/DM, and in controls. **CTGF** levels in patients with dSSc were significantly higher than those in patients with lSSc. As for clinical correlation of **CTGF**, SSc

patients with elevated **CTGF** had pulmonary fibrosis, decreased DLCO, and decreased vital capacity more frequently than those with normal **CTGF** levels. Further, DLCO and vital capacity were inversely and directly correlated with serum **CTGF** levels in patients with SSc. The dSSc patients with disease duration of 1-3 years had significantly elevated levels of **CTGF** compared with dSSc patients with duration < 1 year or more than 3 years. Conclusion. Serum **CTGF** levels were increased in patients with SSc, and correlated with the extent of skin sclerosis and the severity of pulmonary fibrosis. In addition, it appears that production of **CTGF** is involved in the development or maintenance of fibrosis rather than in initiation of fibrosis in SSc. These data suggest that **CTGF** plays a critical role in the development of fibrosis in SSc.

L14 ANSWER 4 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
2001:299415 Document No.: PREV200100299415. Integrin alphaMbeta2 acts as an adhesion receptor on peripheral blood monocytes and THP-1 cells for Cyr61 and connective tissue growth factor. Schober, Joseph M. (1); Lau, Lester F.; Ye, Richard (1); Ugarova, Tatiana P.; Lam, Stephen C.-T. (1). (1) Pharmacology, University of Illinois, Chicago, IL USA. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 18a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology. ISSN: 0006-4971. Language: English. Summary Language: English.

AB Cyr61 and connective tissue growth factor (**CTGF**) are growth factor-inducible immediate-early gene products found in normal blood vessel walls, advanced atherosclerotic lesions and healing cutaneous wounds. We previously showed that the adhesion of endothelial cells, platelets and fibroblasts to these matricellular proteins is mediated by integrin receptors. Because monocyte adhesion is important for inflammation, wound healing and atherosclerosis, we examined the adhesion of isolated peripheral blood monocytes (PBMC) and THP-1 cells to microtiter wells coated with Cyr61 or **CTGF**. Both PBMC and THP-1 cells adhered in a dose-dependent manner to Cyr61- and **CTGF**-coated wells. Moreover, stimulation of THP-1 cells with 20 μ M ADP caused a 6- to 10-fold increase in cell adhesion to both proteins. Time course studies showed that THP-1 cell adhesion to Cyr61 was transient, peaking at 20-30 minutes and declining thereafter. In inhibition studies, while EDTA completely blocked THP-1 cell adhesion to Cyr61, GRGDSP and echistatin had no effect. These data suggest the involvement of an RDG-insensitive integrin receptor. Using **monoclonal antibodies** specific for integrin subunits, we found that the adhesion of THP-1 cells and PBMC to Cyr61 and **CTGF** was specifically blocked by YFC118.3 (anti-beta2), and by 44a and 2LPM19c (anti-alphaM). In contrast, mouse IgG and 6S6 (anti-beta1) had no effect. Thus, monocyte adhesion to Cyr61 and **CTGF** is mediated by integrin alphaMbeta2. Consistent with the cell adhesion data, a GST-fusion protein containing the I-domain of the alphaM subunit bound specifically to immobilized Cyr61 and **CTGF**, and the binding was completely blocked by 2LPM19c (anti-alphaM) but not by YFC118.3 (anti-beta2). Collectively, these results identified integrin alphaMbeta2 as an adhesion receptor on monocytes for Cyr61 and **CTGF**. Since these proteins are synthesized by vascular smooth muscle cells, the interaction of monocytes with these novel extracellular matrix proteins may have an important implication in the physiological function of monocytes.

L14 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2002 ACS
1999:460440 Document No. 131:101260 **Monoclonal antibody** against connective tissue growth factor and medicinal uses thereof. Tamatani, Takuya; Tezuka, Katsunari; Sakamoto, Shinji; Takigawa, Masaharu (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9933878 A1 19990708, 212 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183 19981215.

AB Disclosed is a **human monoclonal antibody** useful for remedying various diseases caused by **human** connective tissue growth factor (hCTGF), and preventing the onset of hCTGF-assocd. diseases. Also, disclosed are various **monoclonal antibodies** having various characteristics against various mammalian connective tissue growth factors (mCTGFs) useful for detecting and assaying mCTGFs present in the body fluids of mammals suffering from mCTGF-assocd. diseases. The **CTGF-assocd.** diseases include cell proliferation-accompanying diseases of or fibrosis of lung, hear, liver, kidney, brain, neck, pancreas, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue, and blood vessel. Thus, **human CTGF** (242-252) peptide Cys-Glu-Ala-Asp-Leu-Glu-Asn-Ile-Lys was synthesized and mixed with Freund's complete adjuvant for immunization to raise polyclonal **antibody** in rabbits. Similarly, **monoclonal anti-hCTGF** and mouse **CTGF antibodies** and producing hybridomas were prep'd. Prep'd. **antibodies** were tested for cross binding reactivity and were used for affinity (column) chromatog. purifn. of mammalian **CTGFs** and treatment of tissue fibrosis in mice model. Mol. cloning of prep'd. **human monoclonal anti-hCTGF antibody** was performed and sequences of single (heavy and light) chain fragments were detd. ELISA with the prep'd. **antibodies** and fragments was used for detecting serum or synovial **CTGF** in patients with biliary duct obstruction, rheumatoid vasculitis, malignant rheumatoid arthritis, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis.

L14 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2002 ACS
1999:299520 Document No. 130:321593 Cloning and cDNA sequences for **human** and murine Wnt-1-induced secreted (WISP) polypeptides. Botstein, David A.; Cohen, Robert L.; Gurney, Austin L.; Hillan, Kenneth; Lawrence, David A.; Levine, Arnold J.; Pennica, Diane; Roy, Margaret Ann; Goddard, Audrey; Wood, William I. (Genentech, Inc., USA). PCT Int. Appl. WO 9921998 A1 19990506, 284 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US22991 19981029. PRIORITY: US 1997-63704 19971029; US 1998-73612 19980203; US 1998-81695 19980414.

AB Wnt-1-induced secreted proteins (WISPs) are provided, whose genes are induced at least by Wnt-1. Several putative Wnt-1-induced genes (WISP1, WISP2, WISP3) were identified at the mRNA level in a high-throughput cDNA subtraction expt. The cDNA clones encode novel polypeptides having homol. to **CTGF**. The genes downstream of Wnt-1 signaling in vertebrates presumably function in tumorigenesis. WISP-1 is expressed in embryonic skeletal mesenchyme and at sites of bone formation, is likely to play a role in osteogenesis, and may be involved in repair after injury. Also provided are nucleic acid mols. encoding those polypeptides, as well as vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide mols. comprising the polypeptides fused to heterologous polypeptide sequences, **antibodies** which bind to the polypeptides, and methods for producing the polypeptides.

L14 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2002 ACS

1999:220010 Document No. 130:251226 Neovascularization inhibitor. Takigawa, Masaharu; Nakanishi, Tohru; Shimo, Tsuyoshi (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9913910 A1 19990325, 53 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP4124 19980911. PRIORITY: JP 1997-267943 19970912; JP 1998-267388 19980904.

AB A medicinal compn. contg. an **antibody** having a reactivity with **human CTGF** (connective tissue growth factor) has been found out to inhibit the proliferation and migration of vascular endothelial cells and, moreover, neovascularization. It is highly useful in treating diseases and symptoms caused by the proliferation and migration of vascular endothelial cells or neovascularization (for example, diabetic retinopathy, arteriosclerosis, arterial constriction, chronic articular rheumatism, psoriasis, sclerema, glaucoma, proliferation or metastasis of tumor, and inflammation in various organs). Thus, recombinant **human CTGF** was constructed, expressed in HeLa cells, and tested for vascular endothelial cell proliferation and migration-promoting activity. Rabbit **monoclonal anti-human CTGF antibody** was prep'd. using CEADLEIK as immunogen, and tested for vascular endothelial cell proliferation and migration-inhibiting activity. In addn., transgenic mice were used for raising **human monoclonal anti-human CTGF antibodies** and hybridomas producing them.

L14 ANSWER 8 OF 13 MEDLINE

DUPLICATE 1

1999377072 Document Number: 99377072. PubMed ID: 10446209.

Activation-dependent adhesion of **human** platelets to Cyr61 and Fisp12/mouse connective tissue growth factor is mediated through integrin alpha(IIb)beta(3). Jedsadayanmata A; Chen C C; Kireeva M L; Lau L F; Lam S C. (Department of Pharmacology, University of Illinois, Chicago, Illinois 60612, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Aug 20) 274 (34) 24321-7. Journal code: 2985121R. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Cyr61 and connective tissue growth factor (**CTGF**), members of a newly identified family of extracellular matrix-associated signaling molecules, are found to mediate cell adhesion, promote cell migration and enhance growth factor-induced cell proliferation in vitro, and induce angiogenesis in vivo. We previously showed that vascular endothelial cell adhesion and migration to Cyr61 and Fisp12 (mouse **CTGF**) are mediated through integrin alpha(v)beta(3). Both Cyr61 and Fisp12/mCTGF are present in normal blood vessel walls, and it has been demonstrated that **CTGF** is overexpressed in advanced atherosclerotic lesions. In the present study, we examined whether Cyr61 and Fisp12/mCTGF could serve as substrates for platelet adhesion. Agonist (ADP, thrombin, or U46619)-stimulated but not resting platelets adhered to both Cyr61 and Fisp12/mCTGF, and this process was completely inhibited by prostaglandin I(2), which prevents platelet activation. The specificity of Cyr61- and Fisp12/mCTGF-mediated platelet adhesion was demonstrated by specific inhibition of this process with polyclonal anti-Cyr61 and anti-Fisp12/mCTGF **antibodies**, respectively. The adhesion of ADP-activated platelets to both proteins was divalent cation-dependent and was blocked by RGDS, HHLGGAKQAGDV, or echistatin, but not by RGES. Furthermore, this process was specifically inhibited by the **monoclonal antibody** AP-2 (anti-alpha(IIb)beta(3)), but not by LM609 (anti-alpha(v)beta(3)), indicating that the interaction is mediated through integrin alpha(IIb)beta(3). In a solid phase binding

assay, activated alpha(IIb)beta(3), purified by RGD affinity chromatography, bound to immobilized Cyr61 and Fisp12/mCTGF in a dose-dependent and RGD-inhibitable manner. In contrast, unactivated alpha(IIb)beta(3) failed to bind to either protein. Collectively, these findings identify Cyr61 and Fisp12/mCTGF as two novel activation-dependent adhesive ligands for the integrin alpha(IIb)beta(3) on **human** platelets, and implicate a functional role for these proteins in hemostasis and thrombosis.

L14 ANSWER 9 OF 13 SCISEARCH COPYRIGHT 2002 ISI (R)

1999:659482 The Genuine Article (R) Number: 228UC. Insulin-like growth factor binding protein-4 proteolytic degradation in ovine preovulatory follicles: Studies of underlying mechanisms. Mazerbourg S; Zapf J; Bar R S; Brigstock D R; Lalou C; Binoux M; Monget P (Reprint). INRA, STN PHYSIOL REPRODUCT MAMMIFERES DOMEST, CNRS, URA 1291, F-37380 NOUZILLY, FRANCE (Reprint); INRA, STN PHYSIOL REPRODUCT MAMMIFERES DOMEST, CNRS, URA 1291, F-37380 NOUZILLY, FRANCE; UNIV ZURICH HOSP, DEPT MED, CH-8091 ZURICH, SWITZERLAND; UNIV IOWA, DEPT INTERNAL MED, IOWA CITY, IA 52246; CHILDRENS HOSP, WEXNER INST PEDIAT RES, DEPT SURG, DIV PEDIAT SURG, COLUMBUS, OH 43205; HOP ST ANTOINE, INST NATL SANTE & RECH MED, UNITE RECH REGULAT CROISSANCE, U142, F-75012 PARIS, FRANCE. ENDOCRINOLOGY (SEP 1999) Vol. 140, No. 9, pp. 4175-4184. Publisher: ENDOCRINE SOC. 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110. ISSN: 0013-7227. Pub. country: FRANCE; SWITZERLAND; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The regulation of insulin-like growth factor binding protein (IGFBP)-4 proteolytic degradation by insulin-like growth factors (IGFs) has been largely studied in vitro, but not in vivo. The aim of this study was to investigate the involvement of IGFs, IGFBP-2, IGFBP-3, and IGFBP-3 proteolytic fragments in the regulation of IGFBP-4 proteolytic activity in ovine ovarian follicles. Follicular fluid from preovulatory follicles contains proteolytic activity degrading exogenous IGFBP-4. The addition of an excess of IGF-I enhanced IGFBP-4 proteolytic degradation, whereas addition of IGFBP-2 or -3 or **monoclonal antibodies** against IGF-I and -II dose dependently inhibited IGFBP-4 proteolytic degradation. IGF-I and IGF-II, but not LongR3-IGF-I, reversed this inhibition in a dose-dependent manner. C-terminal, but not N-terminal, proteolytic fragments derived from IGFBP-3 (aa 161-264), as well as heparin-binding domain-containing peptides derived from the C-terminal domain of IGFBP-3 and -5 also induced the inhibition of IGFBP-4 proteolytic degradation. Other heparin-binding domain-containing peptides derived from the connective tissue growth factor (CTGF) and from proteins not related to IGFBP, heparan/heparin interacting protein (HIP) and vitronectin, but not from p36 subunit of annexin II tetramer, inhibited IGFBP-4 degradation. Furthermore, IGFBP-3, mutated on its heparin-binding domain, was not able to inhibit IGFBP-4 proteolytic degradation. So, in ovine preovulatory follicles, IGFBP-4 proteolytic degradation both 1) depends on IGFs, and 2) is inhibited by IGFBP-3 via its C-terminal heparin-binding domain as well as by heparin-binding domain containing peptides. These data suggest that in early atretic follicles, the increase in IGFBP-2 participates in the decrease in IGFBP-4 degradation. In late atretic follicles, the increase in the levels of C-terminal IGFBP-3 proteolytic fragments, generated by IGFBP-3 degradation, as well as the increase in IGFBP-5 expression would strengthen the inhibition of IGFBP-4 degradation. This inhibition might be partly mediated by direct interaction of IGFBP-4 proteinase(s) and heparin-binding domain within the C-terminal region from IGFBP-3 and -5.

L14 ANSWER 10 OF 13 MEDLINE

DUPLICATE 2

1999008896 Document Number: 99008896. PubMed ID: 9790981. Establishment of the enzyme-linked immunosorbent assay for connective tissue growth factor (CTGF) and its detection in the sera of biliary atresia. Tamatani T; Kobayashi H; Tezuka K; Sakamoto S; Suzuki K; Nakanishi T;

Takigawa M; Miyano T. (Pharmaceutical Frontier Research Laboratories, JT Inc., Yokohama, Kanagawa, 236-0004, Japan.. tamatani@ikrl.jti.co.jp) . BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Oct 29) 251 (3) 748-52. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Connective tissue growth factor (**CTGF**) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine **monoclonal antibodies** against **CTGF** and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of **CTGF**. By using the ELISA, we confirmed that **CTGF** was specifically induced in **human** fibroblasts by TGF-beta but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of **CTGF** were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that **CTGF** is potentially a useful parameter for monitoring certain types of fibrotic disorders.

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L14 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC. 1999:459 Document No.: PREV199900000459. Establishment of the enzyme-linked immunosorbent assay for connective tissue growth factor (**CTGF**) and its detection in the sera of biliary atresia. Tamatani, Takuya; Kobayashi, Hiroyuki; Tezuka, Katsunari; Sakamoto, Shinji; Suzuki, Kensuke; Nakanishi, Tohru; Takigawa, Masaharu; Miyano, Takeshi. Pharmaceutical Frontier Res. Lab., JT Inc. 1-13-2 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004 Japan. Biochemical and Biophysical Research Communications, (Oct. 29, 1998) Vol. 25, No. 3, pp. 748-752. ISSN: 0006-291X. Language: English.

AB Connective tissue growth factor (**CTGF**) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine **monoclonal antibodies** against **CTGF** and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of **CTGF**. By using the ELISA, we confirmed that **CTGF** was specifically induced in **human** fibroblasts by TGF-beta but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of **CTGF** were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that **CTGF** is potentially a useful parameter for monitoring certain types of fibrotic disorders.

L14 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2002 ACS 1995:599637 Document No. 123:7874 Connective tissue growth factor (**CTGF**) and **antibodies** to **CTGF**. Grotendorst, Gary R.; Bradham, Jr Douglas M. (University of South Florida, USA). U.S. US 5408040 A 19950418, 12 pp. Cont. of U.S. Ser. No. 752,427, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1993-167628 19931214. PRIORITY: US 1991-752427 19910830.

AB A novel chemotactic and mitogenic protein, Connective Tissue Growth Factor (**CTGF**), a polynucleotide that encodes **CTGF** and **antibodies** that bind to **CTGF** are provided. Diagnostic and therapeutic methods using **CTGF** are also described. For example, **CTGF** was partially purified from **human** umbilical vein endothelial cells with an affinity column contg. immobilized anti-PDGF IgG, the chemotactic and mitogenic activities of **CTGF** but not PDGF were identified, binding of the **CTGF** to PDGF receptor in endothelial cells was assayed, the mol. cloning and in vitro transcription and translation of **CTGF** were described, and the nucleic acid sequence of **CTGF** was detd. and amino acid sequence was deduced.

L14 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2002 ACS 1993:165635 Document No. 118:165635 The nov gene of chickens, its cloning and use in the diagnosis of cancer. Perbal, Bernard; Martinerie, Cecile

(Centre National de la Recherche Scientifique, Fr.). PCT Int. Appl. WO 9300430 A1 19930107, 67 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE. (French). CODEN: PIXXD2. APPLICATION: WO 1992-FR589 19920625. PRIORITY: FR 1991-7807 19910625.

AB The nov gene of poultry, involved in the development of nephroblastoma, is cloned and characterized for use in diagnosis. A cDNA for a transcript more strongly expressed in tumor cells than normal cells was obtained by differential screening of a cDNA bank fibroblasts of 13 day embryos. The cDNA was used to screen a **human** placental DNA library for the corresponding **human** sequences. The **human** gene showed a tissue-specific pattern of expression.

=> s (tamatani t?/au or tezuka k?/au or sakamoto s?/au or takigawa m?/au)
L15 10715 (TAMATANI T?/AU OR TEZUKA K?/AU OR SAKAMOTO S?/AU OR TAKIGAWA M?/AU)

=> s 115 and CTGF
L16 159 L15 AND CTGF

=> s 116 and antibody
L17 29 L16 AND ANTIBODY

=> dup remove 117
PROCESSING COMPLETED FOR L17
L18 10 DUP REMOVE L17 (19 DUPLICATES REMOVED)

=> d 118 1-10 cbib abs

L18 ANSWER 1 OF 10 MEDLINE
2002306757 Document Number: 22011758. PubMed ID: 12016149. Connective tissue growth factor increased by hypoxia may initiate angiogenesis in collaboration with matrix metalloproteinases. Kondo Seiji; Kubota Satoshi; Shimo Tsuyoshi; Nishida Takashi; Yosimichi Gen; Eguchi Takanori; Sugahara Toshio; **Takigawa Masaharu**. (Department of Biochemistry and Molecular Dentistry, Okayama University Graduate School of Medicine and Dentistry and Biodental Research Center, Okayama University Dental School, 2-5-1 Shikata-cho, Okayama 700-8525, Japan.) CARCINOGENESIS, (2002 May) 23 (5) 769-76. Journal code: 8008055. ISSN: 0143-3334. Pub. country: England: United Kingdom. Language: English.

AB Connective tissue growth factor (**CTGF**) is known to be a potent angiogenic factor. Here we investigated how **CTGF** and matrix metalloproteinases (MMPs) are involved in the early stage of hypoxia-induced angiogenesis using human breast cancer cell line, MDA231, and vascular endothelial cells. Hypoxic stimulation (5% O₂) of MDA231 cells increased their steady-state level of **ctgf** mRNA by approximately 2-fold within 1.5 h, and the levels remained at a plateau up to 6 h, and then decreased by 12 h as compared with the cells cultured under the normoxic condition. Membrane-type 1 MMP (MT1-MMP) mRNA levels was also increased within a few hours of the exposure to hypoxia. Indeed, ELISA revealed that the **CTGF** protein/cell in medium conditioned by MDA231 cells exposed to hypoxia was maximally greater at 24 h than in the medium from normoxic cultures and that the secretion rate (supernatant **CTGF**/cell layer **CTGF**) increased in a time-dependent manner from 24 to 72 h of hypoxic exposure. Hypoxic induction of **CTGF** was also confirmed by immunohistochemical analyses. Furthermore, zymogram analysis revealed that the production of active MMP-9 was also induced in MDA231 cells incubated under hypoxic conditions. Finally, we found that recombinant **CTGF** also increased the expression of a number of metalloproteinases that play a role in the vascular invasive processes and decreased the expression of tissue inhibitors of metalloproteinases by vascular endothelial cells. These

findings suggest that hypoxia stimulates MDA231 cells to release **CTGF** as an angiogenic modulator, which initiates the invasive angiogenesis cascade by modulating the balance of extracellular matrix synthesis and degradation via MMPs secreted by endothelial cells in response to **CTGF**. This cascade may play critical roles in the hypoxia-induced neovascularization that accompanies tumor invasion *in vivo*.

L18 ANSWER 2 OF 10 MEDLINE DUPLICATE 1
2001675289 Document Number: 21578182. PubMed ID: 11721179. Involvement of **CTGF**, a hypertrophic chondrocyte-specific gene product, in tumor angiogenesis. Shimo T; Nakanishi T; Nishida T; Asano M; Sasaki A; Kanyama M; Kuboki T; Matsumura T; **Takigawa M**. (Department of Biochemistry and Molecular Dentistry, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan.) ONCOLOGY, (2001) 61 (4) 315-22. Journal code: 0135054. ISSN: 0030-2414. Pub. country: Switzerland. Language: English.

AB Connective tissue growth factor (**CTGF**) is a potent secreted signaling factor which functions in multiple stages of angiogenesis. In the present study, we examined the role of **CTGF** in tumor angiogenesis and made the following observations: (1) Histological analysis of human breast cancer (MDA231) cell and human fibrosarcoma (HT1080) cell xenografts in BALB/c nude mice showed a high level of neovascularization. Human squamous cell carcinoma (A431) xenografts induced only a low level of neovascularization. (2) **CTGF** mRNA was strongly expressed in MDA231 and in HT1080 cells *in vivo* and *in vitro*, but not in A431 cells. (3) **CTGF** protein was markedly produced in MDA231 cells and HT1080 cells and secreted into culture medium, and its production was greater during phases of growth rather than confluence. (4) Production of **CTGF** in bovine aorta endothelial cells was induced by **CTGF**, VEGF, bFGF and TGF-beta. (5) Neovascularization induced by HT1080 cells or MDA231 cells on chicken chorioallantoic membrane was suppressed in the presence of neutralizing **CTGF**-specific polyclonal antibody. These results suggest that **CTGF** regulates progression in tumor angiogenesis and the release or secretion of **CTGF** from tumor cells is essential for the angiogenesis.

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L18 ANSWER 3 OF 10 MEDLINE DUPLICATE 2
2000080284 Document Number: 20080284. PubMed ID: 10614647. Effects of **CTGF/Hcs24**, a product of a hypertrophic chondrocyte-specific gene, on the proliferation and differentiation of chondrocytes in culture. Nakanishi T; Nishida T; Shimo T; Kobayashi K; Kubo T; **Tamatani T**; **Tezuka K**; **Takigawa M**. (Department of Biochemistry and Molecular Dentistry, Biodental Research Center, Okayama University Dental School, Japan.) ENDOCRINOLOGY, (2000 Jan) 141 (1) 264-73. Journal code: 0375040. ISSN: 0013-7227. Pub. country: United States. Language: English.

AB Recently, we cloned a messenger RNA (mRNA) predominantly expressed in chondrocytes from a human chondrosarcoma-derived chondrocytic cell line, HCS-2/8, by differential display PCR and found that its gene, named *hcs24*, was identical with that of connective tissue growth factor (**CTGF**). Here we investigated **CTGF/Hcs24** function in the chondrocytic cell line HCS-2/8 and rabbit growth cartilage (RGC) cells. HCS-2/8 cells transfected with recombinant adenoviruses that generate **CTGF**/Hcs24 sense RNA (mRNA) proliferated more rapidly than HCS-2/8 cells transfected with control adenoviruses. HCS-2/8 cells transfected with recombinant adenoviruses that generate **CTGF/Hcs24** sense RNA expressed more mRNA of aggrecan and type X collagen than the control cells. To elucidate the direct action of **CTGF/Hcs24** on the cells, we transfected HeLa cells with **CTGF/Hcs24** expression vectors, obtained stable transfectants, and purified recombinant **CTGF/Hcs24** protein from conditioned medium of the transfectants.

The recombinant **CTGF/Hcs24** effectively promoted the proliferation of HCS-2/8 cells and RGC cells in a dose-dependent manner and also dose dependently increased proteoglycan synthesis in these cells. In addition, these stimulatory effects of **CTGF/Hcs24** were neutralized by the addition of anti-**CTGF antibodies**. Furthermore, the recombinant **CTGF/Hcs24** effectively increased alkaline phosphatase activity in RGC cells in culture. Moreover, RT-PCR analysis revealed that the recombinant **CTGF/Hcs24** stimulated gene expression of aggrecan and collagen types II and X in RGC cells in culture. These results indicate that **CTGF/Hcs24** directly promotes the proliferation and differentiation of chondrocytes.

L18 ANSWER 4 OF 10 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2000040274 EMBASE Serum levels of connective tissue growth factor are elevated in patients with systemic sclerosis: Association with extent of skin sclerosis and severity of pulmonary fibrosis. Sato S.; Nagaoka T.; Hasegawa M.; **Tamatani T.**; Nakanishi T.; **Takigawa M.**; Takehara K.. Dr. S. Sato, Department of Dermatology, Kanazawa Univ. School of Medicine, 13-1 Takaramachi, Kanazawa, Ishikawa 920-8641, Japan. s-sato@med.kanazawa-u.ac.jp. Journal of Rheumatology 27/1 (149-154) 2000.

Refs: 33.

ISSN: 0315-162X. CODEN: JRHUA. Pub. Country: Canada. Language: English. Summary Language: English.

AB Objective. To determine the serum levels and clinical correlation of connective tissue growth factors (**CTGF**) in patients with systemic sclerosis (SSc). Methods. Serum samples from patients with limited cutaneous SSc (lSSc, n = 32), diffuse cutaneous SSc (dSSc, n = 28), systemic lupus erythematosus (SLE, n = 30), polymyositis/dermatomyositis (PM/DM, n = 20), and healthy control subjects (n = 30) were examined by ELISA for detection of **CTGF**. Results. Serum **CTGF** levels in patients with SSc were significantly higher than those in patients with SLE or PM/DM, and in controls. **CTGF** levels in patients with dSSc were significantly higher than those in patients with lSSc. As for clinical correlation of **CTGF**, SSc patients with elevated **CTGF** had pulmonary fibrosis, decreased DLCO, and decreased vital capacity more frequently than those with normal **CTGF** levels. Further, DLCO and vital capacity were inversely and directly correlated with serum **CTGF** levels in patients with SSc. The dSSc patients with disease duration of 1-3 years had significantly elevated levels of **CTGF** compared with dSSc patients with duration < 1 year or more than 3 years. Conclusion. Serum **CTGF** levels were increased in patients with SSc, and correlated with the extent of skin sclerosis and the severity of pulmonary fibrosis. In addition, it appears that production of **CTGF** is involved in the development or maintenance of fibrosis rather than in initiation of fibrosis in SSc. These data suggest that **CTGF** plays a critical role in the development of fibrosis in SSc.

L18 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS
1999:460440 Document No. 131:101260 Monoclonal **antibody** against connective tissue growth factor and medicinal uses thereof.
Tamatani, Takuya; Tezuka, Katsunari; Sakamoto, Shinji; Takigawa, Masaharu (Japan Tobacco Inc., Japan).
PCT Int. Appl. WO 9933878 A1 19990708, 212 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP5697 19981216. PRIORITY: JP 1997-367699 19971225; JP 1998-356183 19981215.

AB Disclosed is a human monoclonal **antibody** useful for remedying various diseases caused by human connective tissue growth factor (hCTGF), and preventing the onset of hCTGF-assocd. diseases. Also, disclosed are various monoclonal **antibodies** having various characteristics against various mammalian connective tissue growth factors (mCTGFs) useful for detecting and assaying mCTGFs present in the body fluids of mammals suffering from mCTGF-assocd. diseases. The **CTGF**-assocd. diseases include cell proliferation-accompanying diseases of or fibrosis of lung, heart, liver, kidney, brain, neck, pancreas, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue, and blood vessel. Thus, human **CTGF** (242-252) peptide Cys-Glu-Ala-Asp-Leu-Glu-Glu-Asn-Ile-Lys was synthesized and mixed with Freund's complete adjuvant for immunization to raise polyclonal **antibody** in rabbits. Similarly, monoclonal anti-hCTGF and mouse **CTGF antibodies** and producing hybridomas were prep'd. Prep'd. **antibodies** were tested for cross binding reactivity and were used for affinity (column) chromatog. purifn. of mammalian **CTGFs** and treatment of tissue fibrosis in mice model. Mol. cloning of prep'd. human monoclonal anti-hCTGF **antibody** was performed and sequences of single (heavy and light) chain fragments were detd. ELISA with the prep'd. **antibodies** and fragments was used for detecting serum or synovial **CTGF** in patients with biliary duct obstruction, rheumatoid vasculitis, malignant rheumatoid arthritis, psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis.

L18 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2002 ACS

1999:220010 Document No. 130:251226 Neovascularization inhibitor.

Takigawa, Masaharu; Nakanishi, Tohru; Shimo, Tsuyoshi (Japan Tobacco Inc., Japan). PCT Int. Appl. WO 9913910 A1 19990325, 53 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1998-JP4124 19980911. PRIORITY: JP 1997-267943 19970912; JP 1998-267388 19980904.

AB A medicinal compn. contg. an **antibody** having a reactivity with human **CTGF** (connective tissue growth factor) has been found out to inhibit the proliferation and migration of vascular endothelial cells and, moreover, neovascularization. It is highly useful in treating diseases and symptoms caused by the proliferation and migration of vascular endothelial cells or neovascularization (for example, diabetic retinopathy, arteriosclerosis, arterial constriction, chronic articular rheumatism, psoriasis, sclerema, glaucoma, proliferation or metastasis of tumor, and inflammation in various organs). Thus, recombinant human **CTGF** was constructed, expressed in HeLa cells, and tested for vascular endothelial cell proliferation and migration-promoting activity. Rabbit monoclonal anti-human **CTGF antibody** was prep'd. using CEADLEEK as immunogen, and tested for vascular endothelial cell proliferation and migration-inhibiting activity. In addn., transgenic mice were used for raising human monoclonal anti-human **CTGF antibodies** and hybridomas producing them.

L18 ANSWER 7 OF 10 MEDLINE

DUPLICATE 3

1999321851 Document Number: 99321851. PubMed ID: 10393331. Connective tissue growth factor induces the proliferation, migration, and tube formation of vascular endothelial cells in vitro, and angiogenesis in vivo. Shimo T; Nakanishi T; Nishida T; Asano M; Kanyama M; Kuboki T; Tamatani T; Tezuka K; Takemura M; Matsumura T; Takigawa M. (Department of Biochemistry and Molecular Dentistry,

Okayama University Dental School, Okayama, 700-8525, Japan.) JOURNAL OF BIOCHEMISTRY, (1999 Jul) 126 (1) 137-45. Journal code: 0376600. ISSN: 0021-924X. Pub. country: Japan. Language: English.

AB Connective tissue growth factor (**CTGF**) is a novel cysteine-rich, secreted protein. Recently, we found that inhibition of the endogenous expression of **CTGF** by its antisense oligonucleotide and antisense RNA suppresses the proliferation and migration of vascular endothelial cells. In the present study, the following observations demonstrated the angiogenic function of **CTGF** *in vitro* and *in vivo*: (i) purified recombinant **CTGF** (rCTGF) promoted the adhesion, proliferation and migration of vascular endothelial cells in a dose-dependent manner under serum-free conditions, and these effects were inhibited by anti-**CTGF antibodies**; (ii) rCTGF markedly induced the tube formation of vascular endothelial cells, and this effect was stronger than that of basic fibroblast growth factor or vascular endothelial growth factor; (iii) application of rCTGF to the chicken chorioallantoic membrane resulted in a gross angiogenic response, and this effect was also inhibited by anti-**CTGF antibodies**. (iv) rCTGF injected with collagen gel into the backs of mice induced strong angiogenesis *in vivo*. These findings indicate that **CTGF** is a novel, potent angiogenesis factor which functions in multi-stages in this process.

L18 ANSWER 8 OF 10 MEDLINE DUPLICATE 4
1999008896 Document Number: 99008896. PubMed ID: 9790981. Establishment of the enzyme-linked immunosorbent assay for connective tissue growth factor (**CTGF**) and its detection in the sera of biliary atresia.

Tamatani T; Kobayashi H; Tezuka K; Sakamoto S; Suzuki K; Nakanishi T; Takigawa M; Miyano T. (Pharmaceutical Frontier Research Laboratories, JT Inc., Yokohama, Kanagawa, 236-0004, Japan.. tamatani@ikrl.jti.co.jp) . BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Oct 29) 251 (3) 748-52. Journal code: 0372516. ISSN: 0006-291X. Pub. country: United States. Language: English.

AB Connective tissue growth factor (**CTGF**) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine monoclonal **antibodies** against **CTGF** and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of **CTGF**. By using the ELISA, we confirmed that **CTGF** was specifically induced in human fibroblasts by TGF-beta but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of **CTGF** were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that **CTGF** is potentially a useful parameter for monitoring certain types of fibrotic disorders.

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L18 ANSWER 9 OF 10 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:459 Document No.: PREV199900000459. Establishment of the enzyme-linked immunosorbent assay for connective tissue growth factor (**CTGF**) and its detection in the sera of biliary atresia. **Tamatani, Takuya** ; **Kobayashi, Hiroyuki**; **Tezuka, Katsunari**; **Sakamoto, Shinji**; **Suzuki, Kensuke**; **Nakanishi, Tohru**; **Takigawa, Masaharu** ; **Miyano, Takeshi**. Pharmaceutical Frontier Res. Lab., JT Inc. 1-13-2 Fukuura, Kanazawa-ku, Yokohama, Kanagawa 236-0004 Japan. Biochemical and Biophysical Research Communications, (Oct. 29, 1998) Vol. 25, No. 3, pp. 748-752. ISSN: 0006-291X. Language: English.

AB Connective tissue growth factor (**CTGF**) is a mitogenic, chemotactic, and cell matrix-inducing factor for fibroblasts. We generated murine monoclonal **antibodies** against **CTGF** and established a sandwich enzyme-linked immunosorbent assay (ELISA) for detection of **CTGF**. By using the ELISA, we confirmed that **CTGF** was specifically induced in human fibroblasts by TGF-beta but not by PDGF, FGF, IGF-I, or EGF. We also found that the serum levels of

CTGF were significantly correlated with the progression of hepatic fibrosis in biliary atresia. These results indicated that **CTGF** is potentially a useful parameter for monitoring certain types of fibrotic disorders.

L18 ANSWER 10 OF 10 MEDLINE DUPLICATE 5
1998309859 Document Number: 98309859. PubMed ID: 9644255. Inhibition of endogenous expression of connective tissue growth factor by its antisense oligonucleotide and antisense RNA suppresses proliferation and migration of vascular endothelial cells. Shimo T; Nakanishi T; Kimura Y; Nishida T; Ishizeki K; Matsumura T; **Takigawa M.** (Department of Biochemistry and Molecular Dentistry Iwate Medical University School of Dentistry, Morioka, 020-0021, Japan.) JOURNAL OF BIOCHEMISTRY, (1998 Jul) 124 (1) 130-40. Journal code: 0376600. ISSN: 0021-924X. Pub. country: Japan. Language: English.

AB Previously, we cloned an mRNA predominantly expressed in hypertrophic chondrocytes by differential display-PCR from a human chondrosarcoma-derived chondrocytic cell line (HCS-2/8) that is identical to that of connective tissue growth factor (**CTGF**). In the present study, we investigated the roles of **CTGF** in the proliferation and migration of vascular endothelial cells using its antisense oligonucleotide and antisense RNA, because angiogenesis into the hypertrophic zone of cartilage occurs at the final step of endochondral ossification. Immunohistochemical and immunofluorescence techniques revealed that not only hypertrophic chondrocytes but also endothelial cells in the cost-chondral junctions of mouse ribs were stained with an anti-**CTGF antibody** in vivo. Northern blot analysis revealed that **CTGF** was strongly expressed in chondrocytic cells as well as bovine aorta endothelial (BAE) cells in culture, but not in other types of cells such as osteoblastic cells. Its expression in BAE cells was greater in the growing phase than in the confluent phase. When one-half of a monolayer of a confluent culture of BAE cells had been peeled off, only the cells proliferating and extending into the vacant area were stained with the anti-**CTGF antibody**. The addition of an antisense oligonucleotide inhibited the proliferation and extension of the BAE cells into the vacant area. The antisense oligonucleotide also inhibited the proliferation of BAE cells in the rapidly proliferating phase. In a Boyden chamber assay, pretreatment with the antisense oligonucleotide markedly inhibited the migration of BAE cells. Furthermore, the abilities to proliferate and migrate of BAE cells, which were stably transfected with expression vectors that generate the antisense RNA of **CTGF** cDNA, were markedly lower than those of the control. These findings suggest that endogenous **CTGF** expression is involved in the proliferation and migration of BAE cells.

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FULL ESTIMATED COST	97.80	98.01
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